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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Mueting Raasch & Gebhardt PA
PO Box 581415
Minneapolis, MN 55458-1415

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,802	BOLDOGH ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Remailing pursuant to MPEP 710.06

1. This Office Action is a replacement of the Office Action mailed (17 February 2004) which did not listed the Janusz et al. (1987) Immunoregulatory Properties of Synthetic Peptides, Fragments of a Proline-Rich Polypeptide (PRP) from Ovine Colostrum." Molecular Immunology **24**(10): 1029-1031 reference on the PTO-892 nor did it provide a copy. Nancy Johnson called this to the attention of the Examiner on 5 May 2004 and the Office Action is hereby replaced. The period for reply is controlled by the instant Office Action.

Status of Application, Amendments, and/or Claims

2. The Office Action mailed 15 August 2003 was improper because it did not fully address each and every limitation of all the pending claims. Due to the length and incomplete prosecution, all previously made Rejections and Objections not herein maintained are *withdrawn*. Prosecution on the merits is hereby reopened to respond to Applicant's After Final Amendment (17 November 2003) as a courtesy to Applicant at SPE Kunz's behest. It does not in any way, shape, or form reflect upon the validity of past rejections or the persuasiveness of any arguments and Declarations supplied by Applicant.

3. All previous Amendments are hereby *entered*.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

5. The Restriction Requirement mailed 18 June 2002 is still in effect. Applicant's traversal is noted. Upon reaching allowable subject matter all 34 sequences presented will be rejoined into the allowable subject matter.

Claim Objections

6. Claims **1-17** are objected to for reciting non-elected subject matter.

Non-Statutory Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
>
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
>
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims **1-17** are rejected under the judicially created doctrine of double patenting over claims 1-16 of U. S. Patent No. 6,500,798 B1 (31 December 2002) Stanton *et al.* since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

8. The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows. Both the instant application and US 6,500,798 encompass a method of administering colostrinin, a constituent peptide thereof, active analogs as defined in the claims, and 34 peptides, all of which are identical. Therefore regardless of the goal of the preamble the same compounds are being administered to the same population and will have the same effects. Therefore both the instant Application and US 6,500,798 encompass the same invention [See *Ex parte Novitski*, **26 USPQ2d 1389** (Bd. Pat. App. & Inter. 1993)].

Provisional Non-Statutory Double Patenting

9. Claims **1-17** are rejected under the judicially created doctrine of double patenting over claims 20-35 of Application 09/641,801 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

10. The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows. Both the instant application and Application No. 09/641,801 encompass a method of administering colostrinin, a constituent peptide thereof, active analogs as defined in the claims, and 34 peptides, all of which are identical. Therefore regardless of the goal of the preamble the same compounds are being administered to the same population and will have the same effects. Therefore both the instant Application and Application No. 09/641,801 encompass the same invention [See *Ex parte Novitski*, **26 USPQ2d 1389** (Bd. Pat. App. & Inter. 1993)].

Claim Rejections - 35 USC § 112

11. Claims **1-8** and **16** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an in vitro method for promoting neuronal cell differentiation comprising contacting pluripotent cells from the nervous system*, does not reasonably provide enablement for *practicing said method in vivo, in a patient, or using any other cell type.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **use** the invention commensurate in scope with these claims. This rejection is maintained essentially for the reasons set forth at ¶8-17 pp. 3-7 of the previous Office Action (15 August 2003).

12. Applicant traverses this rejection in the response filed 17 November 2003 (After Final Response, pp. 3-8) on the following grounds: **(a)** the correlation between the *in vitro* model systems provided by PC12 and SH-SY5Y cell lines and *in vivo* results are well accepted, **(b)** Examiner has not described "various complications" involved in neuronal differentiation, **(c)** Applicant has requested clarification on the Examiner's rejection on the subject of preparing and administering colostrinin, constituent peptides thereof, SEQ ID NO: 2, and active analogs as detailed in the claims, **(d)** the Examiner is inappropriately requiring the Applicant to present data from *in vivo* animal experiments or human clinical trials, and **(e)** the data presented by Popik *et al.* and Inglot *et al.* have been taken out of context and Applicant insists that the Examiner substantiate his position with credible evidence and/or reasoned scientific arguments.

13. On "**(a)**", Applicant has made the assertion that evidence from *in vitro* experiments with PC12 and SH-SY5Y cell lines are accepted. This is not the case. No evidence, present in the art,

the Specification, or the Declaration of G. John Stanton under 37 C.F.R. §1.132 filed 7 January 2003 (Paper No. 13) would lead the skilled artisan to this conclusion. The fact remains as follows. Applicant has practiced the claimed invention only in *in vitro* with two cell lines, PC12 and SH-SY5Y. No reasonable nexus can be made between *in vitro* experiments and an *in vivo* based solely on this assertion. Neither the specification nor the prior art suggests that neuronal cell differentiation can be performed in patients (i.e. "*in vivo*"). For instance, Inglot et al. [(1996) "Colostrinine: a proline-rich polypeptide from ovine colostrums is a modest cytokine inducer in human leukocytes." Arch. Immunol. Ther. Exp. (Warsz). 44(4): 215-224 (**IDS**)] teaches that colostrinin or constituent peptide thereof [PRP, NP] induces IFN and TNF-α production in human peripheral blood mononuclear leukocytes (PBL) *in vitro* (pp. 217 Table 1; pp. 218 Table 3). In light of this evidence, a person of ordinary skill in the art would doubt that these colostrinin analogs were inducing or acting as "*neuronal cell regulators*" and changing "*the cells in morphology to form neuronal cells*" (Claim 1 of the instant application). Thus the claimed full scope of the invention is contrary to the teachings of the prior art. Also neither reference suggests or teaches that it should be presumed that it would enable *in vivo* use (see MPEP §2164.02). The references cited in the Response filed 17 November 2003 fail to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office (Information Disclosure Statement). The information referred to therein has not been considered.

14. On "**(b)**", the "various complications" referred to by the Examiner are well known and notorious in the art. The phrase "neuronal cells" constitutes a large and diverse genus. While a skilled artisan could identify neuronal or indeed, neural cells, the responses of each particular

member of these large geneses would vary. Despite the commonalities among morphology and cytoskeletal components, neuronal cells vary in their response to cell signaling molecules. In addition, these differences are based on their anatomical origin, their state of differentiation (precursor versus adult), their neurochemical profile, and whether they are neurons or glia [see Kandel et al. (2002) "Principles of Neural Science."4th Ed. pp. 67-81, 85-86; Bikfalvi et al. (February 1997) "Biological Roles of Fibroblast Growth Factor-2" Endocrine Reviews 18(1): 26-45, especially Section F; Rao (1999) "Multipotent and Restricted Precursors in the Central Nervous System." The Anatomical Record (NEW ANAT.) 257: 137-148, and Gage *et al.* "Isolation, Characterization, and Use of Stem Cells from the CNS." Ann. Rev. Neurosci. **18**: 159-192]. Further Applicant is invited to review Columns 1-7 of US 6,040,180 (21 March 2000) Johe which reviews the difficulties and variance found in cell differentiation and states:

15. "Results such as these illustrate that identifying CNS stem cells, defining conditions that stable maintain CNS stem cell properties for long-term, and controlling their differentiation into mature cell types are neither obvious nor predictable to those skilled in this art." (Col. 7 lines 54-60)

16. Therefore the difficulty and unpredictability discussed by the Examiner in the art of cell differentiation does not constitute opinion but is supported by the references above.

17. On "**(c)**", for a complete discussion and rejection on these grounds, Applicant is referred to the written description rejection included herein.

18. On "**(d)**", no such requirement has been made. The Examiner has based the rejection on the unpredictability in the art, the absence of any evidence, and the complexity of the invention. Any supposition that a requirement for additional evidence is improper. The Examiner has only clearly stated the absence of any such data in the Specification and the prior art.

19. On "**(e)**", the Examiner has used the two references, Popik *et al.* and Inglot *et al.*, as examples of the known properties of colostrinin and three of its constituent peptides, PRP, NP, and CVNP as potent immunologically active peptides. The Examiner has used these references under the Wands Factor of "the state of the prior art". Accordingly, Applicant is asserting a new property for an old product; therefore argument is insufficient to establish the activity as claimed (MPEP §2112). In view of the prior art, no nexus between known immunologically active peptides and a "neuronal cell regulator" can be made as no such nexus or teaching is present.

20. On "**(f)**", no evidence or findings are present in the Specification that support the full breadth of the claims as currently presented. No attempt to "discredit" supposed findings in the Specification has been undertaken nor should be implied as "discredit" has negative connotations which are not present.

21. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* use as exemplified in the references herein.

22. The rejection of claims 1-8 and 16 under 35 USC §112 ¶1 is maintained.

23. Claims **9-13** and **17** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained essentially for the reasons set forth at ¶18-23 pp. 7-8 of the previous Office Action (15 August 2003).

24. Applicant traverses this rejection in the response filed 17 November 2003 (After Final Response, pp. 8-10) on the following grounds: **(a)** Examiner has stated an opinion concerning the lack of correlation between *in vitro* results and *in vivo* use, **(b)** Applicant disagrees with the Examiner that the Specification only contains prophetic examples, **(c)** "Applicant does not understand the logic of the Examiner's argument." in view of Popik *et al.*, and **(d)** previously cited references directly support the therapeutic applications of the PC12 and SH-SHSY5Y cell lines.

25. On "**(a)**", the Examiner notes that references are not required to support a *prima facie* case of lack of enablement (see MPEP 2164.04). Therefore the Examiner reiterates herein the accepted understanding in the art that *in vitro* results cannot easily be applied to fully *in vivo* therapeutic use. While the specification and prior art offers sufficient support to the claims that colostrinin and SEQ ID NO: 2 can stimulate cell differentiation in neuronal cells such as PC12 and SHSY5Y *in vitro* no evidence is provided re: successful stimulation of cell differentiation using SEQ ID NO: 2 in animals, successful treatment of human patients wherein cell differentiation was initiated using SEQ ID NO: 2. A skilled artisan would have no reasonable expectation of success that administration of colostrinin or SEQ ID NO: 2 would act as a "*neuronal cell regulator*".

26. On "**(b)**", in regards to Applicant's arguments in response to Office Actions for the instant application, the Applicant has only provided argument. Applicant has continued to assert that colostrinin, its constituent peptides, active analogues, and SEQ ID NO: 2 possess activity as a "neuronal cell regulator" *in vivo* in the absence of data. It is noted that enablement is only

concerned with factual assertions based on evidence. The Examiner respectfully notes that arguments of consul cannot breathe new properties into compounds.

27. On "**(c)**", the Examiner has cited Popik *et al.* as well as other prior art references to demonstrate that the prior art is silent on any "neuronal cell regulator" properties of colostrinin and its constituent peptides (PRP, NP, CVNP). This was done by the Examiner under the rubric of addressing the "Wands Factors", a standard practice in the USPTO when rejecting claims under 35 U.S.C. §112 ¶1 for lack of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)].

28. On "**(d)**", Applicant has demonstrated that colostrinin and a representative number of 34 peptides have a differentiation effect on PC12 and SHY5HY cells. However, said cell lines are not analogous to non-neuronal cells. Thus the use of *in vitro* systems as support for *in vivo* methods, the *in vitro* system as presented in the instant application is not predictive of an *in vivo* method. The *in vitro* system as presented in the instant application is not an art-recognized model system for the therapy claimed. Further the Specification and the Declaration filed in the instant Application can only support what they support. Both have only provided *in vitro* evidence and prophetic consideration of practicing the invention to the full scope of the claims as currently presented. This constitutes an invitation to experiment.

29. In addition, Applicant's arguments revolve around an assertion that colostrinin, its constituent peptides, active analogues thereof, and SEQ ID NO: 2 inherently possess activity, *in vitro* and *in vivo* as a "neuronal cell regulator".

30. The Examiner further notes that Applicant has, in effect, set forth an "inherency argument", alternatively said peptides have the activity because it is inherent. *In re Robertson*,

169 F.3d 743, 745, 49 USPQd 1949, 1950-19851 (Fed. Cir. 1999) states "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily presenting the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" As noted in previous Office Actions, the prior art is silent on any "neuronal cell regulator" activities of colostrinin, its constituent peptides, and active analogues thereof.

31. The Examiner further respectfully notes that the references cited in the Response filed 17 November 2003 fail to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office (Information Disclosure Statement). The information referred to therein has not been considered.

32. The rejection of claims 9-13 and 17 under 35 USC §112 ¶1 is maintained.

33. Claims **14-15** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained essentially for the reasons set forth at ¶24-33 pp. 8-11 of the previous Office Action (15 August 2003).

34. Applicant traverses this rejection in the response filed 17 November 2003 (After Final Response, pp. 8-10) on the following grounds: **(a)** Applicant does not understand the relevance of WO 98/14773, Kruzel *et al.*, and Zimecki *et al.*, **(b)** the Specification adequately demonstrates

the neuronal regulatory effect of colostrinin, constituent peptides thereof, active analogues thereof, and combinations thereof, **(c)** Examiner has included an inappropriate exaggeration in interpreting the claims, and **(d)** previously cited references directly support the therapeutic applications of the PC12 and SH-SHSY5Y cell lines.

35. On "**(a)**", the Examiner has cited WO 98/14773, Kruzel *et al.*, and Zimecki *et al.* to demonstrate that the art is silent on any "neuronal cell regulator" properties of colostrinin and its constituent peptides (PRP, NP, CVNP). This was done by the Examiner under the rubric of addressing the "Wands Factors", a standard practice in the USPTO when rejecting claims under 35 U.S.C. §112 ¶1 for lack of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)].

36. On "**(b)**", Applicant to date has not provided factual evidence that colostrinin, a constituent peptide thereof, or any of the 34 peptides claimed has the property of converting non-functional cells into functional cells. No examples which have been presented throughout the lengthy prosecution have been art-accepted models of "non-functional" cells nor has the Applicant provided any evidence that suggests or implies in any way, shape, or form that colostrinin, a constituent peptide thereof, or any of the 34 peptides claimed has the property of converting non-functional cells into functional cells in an art accepted animal model of "non-functional cells".

37. Also, the Examiner respectfully notes that as currently presented the claims read on reviving dead cells (i.e. "raising the dead"), regenerating cells, transmuting ruptured cells into whole live cells, reconfiguring fragmented/shredded cells, spontaneous generation (as pieces of cellular material may be transformed into functional cells), and other incredible properties. The

Examiner further notes that it is well known in the art that colostrinin is a potent inducer of cytokines and proliferation in immune cells. However, the art is silent, as is the Specification as well as the argument presented by the Applicant that colostrinin and its peptide derivatives have any ability, whether explicit, implicit, or inherent that said peptides may "convert non-functional cells to functional cells".

38. While the specification and prior art offers sufficient support to the claims that colostrinin and its active peptide analog SEQ ID NO: 2 can stimulate cell differentiation in neuronal cell lines such as PC12 and SHSY5Y *in vitro* no evidence is provided re: successful conversion of damaged neuronal cells into function cells using SEQ ID NO: 2, successful treatment of human patients wherein cell revival was initiated using SEQ ID NO: 2. Thus a skilled artisan lacks the guidance necessary to practice the claimed invention of claims 14 and 15 with a reasonable expectation of success.

39. On "**(c)**", the first "Wands Factor" is "the breadth of the claims" [see MPEP §2164.01(a)] and as such any interpretations or reading of the claims is not in fact an exaggeration but a "broad reading" of the scope of the claims. It is clear that the claims as written read on the use of SEQ ID NO: 2 and its functional analogues to revive dead tissue, resurrect deceased patients who have died from brain failure, and repair all known and unknown causes of nonfunctional neurons. This is clearly not supported by the Specification or the prior art and is not intended to be read as an exaggeration.

40. On "**(d)**", although unnecessary [see *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)], the Examiner respectfully cites Chao (20 March 1992) "Growth Factor Signaling: Where is the Specificity?" Cell **68**: 995-997 (**IDS**) discloses that (pp. 995):

41. "A common misconception is that NGF stimulates neuronal cell division. Despite its name, NGF is not mitogenic for neurons. NGF directs neurite outgrowth and guidance to targets; it promotes cell survival in only a few cell populations which include sympathetic and neural crest-derived sensory neurons."

42. In addition,

43. "Simply put, EGF and NGF trigger the same set of early responses, none of which are wholly specific for EGF or NGF."

44. Therefore, a skilled artisan would doubt that a response to colostrinin or SEQ ID NO: by PC12 cells would be considered representative of all cells.

45. As discussed above, colostrinin and its known active analogs have potent cytokine activity. In regards to the effects of colostrinin and its known analogs on cognition or neuronal cells, Popik et al. (29 January 2001) "Cognitive effects of Colostral-Val nonapeptide in aged rats." Behavioral Brain Research 118(2): 201-208] teaches that Colostral-Val nonapeptide CVNP: *Val-Glu-Ser-Tyr-Pro-Leu-Phe-Pro*, 22.2% proline) shows a strong effect on the primary and secondary immune response against SRBC (T-cell dependent antigen) in mice. Also, CVNP, although less potent than full-length colostrinin, did induce production of interferon (INF) and tumor necrosis factor-α (TNF-α) in human peripheral blood leukocytes and whole blood cell cultures. It is also of note that full-length colostrinin, induces maturation and differentiation of murine thymocytes and affects humoral and cellular immune reactions, in both *in vitro* cultures and *in vivo* (pp. 201-202). When administered to aged rats Popik et al. (1997) teaches that CNVP is not believed to have any direct effects on the process of acquisition of spatial memory (such as being a "*neuronal cell regulator*"). Indeed, CVNP and colostrinin had different effects in the studies presented by Popik et al. (1997) (Figures 1-5). Furthermore Popik et al. (1997) attribute the effects of CVNP on the rats to their immunomodulatory properties and not any direct effect

on the nervous system (pp. 306-307). Taking Popik et al. (1997) into account, a skilled artisan would have doubt that colostrinin analogs were inducing acting as "*neuronal cell regulators*" and changing "*the cells in morphology to form neuronal cells*" (Claim 1 of the instant application).

46. Regarding administering SEQ ID NO: 2 and analogs thereof to patients, including humans, is the induction of a state of the immune system of hyporeactivity or tolerance, manifested by the inability to synthesize IFN and TNF-α [WO 98/14773 pp. 20-21 (**IDS**)]. This hyporeactivity or tolerance is temporary and stops after the termination of the administration of colostrinin [WO 98/14773 pp. 20-21 (**IDS**)]. Thus Janusz et al. does not teach that colostrinin has the effect of a "*neuronal cell regulator*" which converts nonfunctional neuronal cells to functional cells.

47. While PC12 and SH-SHY5Y cells are an art-accepted *in vitro* model to study cell differentiation, they are not indicative of the unpredictability and obstacles to practicing the invention *in vivo*. The claims are drawn very broadly to methods of therapy comprising promoting neuronal cell differentiation in a patient including humans (see discussion above). Further, the Applicant has not provided any examples of *in vivo* use of SEQ ID NO: 2 and its functional analogues *in vivo*. The Specification as filed only offers a prophetic example which describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved. Furthermore MPEP §2164.02 states that the lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. This has been put forth in the previous Office Action and in the discussion above.

48. The Examiner respectfully reviews that the art which teaches that colostrinin and its active analogs have activity as cytokines and not neuronal cell regulators. For instance, Kruzel et al. (December 2001) "Towards and Understanding of Biological Role of Colostrinin Peptides." Journal of Molecular Neuroscience 17(3): 379-389 discloses the identification and synthesis of 42 constituent peptide fragments of full-length colostrinin (Table1). Kruzel et al. also teaches that select peptide fragments induce proliferation and cytokine release (Table 3 and Table 4). Kruzel et al. also discloses the usefulness of using colostrinin and constituent peptides for Alzheimer's patients citing the peptide fragment's ability to induce cytokines and reduce oxidative stress but not a role as a "*neuronal cell regulator*" (pp. 388).

49. Furthermore the prior art also teaches that proline-rich polypeptide (PRP), an active analog of colostrinin is useful for treating an autoimmune disease, not neurodegeneration or any nervous system nonfunction. Zimecki et al. [(1991) "Effect of a proline-rich polypeptide (PRP) on the development of hemolytic anemia and survival of New Zealand Black (NZB) mice." Achivum Immunologiae Et Therapiae Experimentalis 39: 461-467 (**IDS**)] teaches that PRP (an active analog of colostrinin with 22.2% proline) induces the differentiation of immature T cells into functionally active T helper and T suppressor cells (pp. 461 and 466). Zimecki et al. (1991) demonstrated that administration of PRP prolonged the life span of mice with an autoimmune disease (Table 1 and 2).

50. The rejection of claims 14-15 under 35 USC §112 ¶1 is maintained.

51. Claims **1-17** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

52. Claims 1, 9, 14, 15, 16, and 17 recite the limitation "constituent peptide" while not claims do not require that the peptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of peptides that is defined by their origin.

53. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of a protein of origin. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

54. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed

invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

55. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003). In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since patent described the compound's desired function of reducing activity of enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

56. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

57. Claims **1-3, 6, 7, 9, 11, 12, 14, 15, 16,** and **17** are rejected under 35 U.S.C. 102(b) as being anticipated by Janusz *et al.* (1987) "Immunoregulatory Properties of Synthetic Peptides, Fragments of a Proline-Rich Polypeptide (PRP) from Ovine Colostrum." Molecular Immunology **24**(10): 1029-1031.

58. The claims are drawn to a method which comprises the step of contacting cells with a "neural cell regulator" therein defined as colostrinin, a constituent peptide thereof, an active analog thereof wherein said analog is required to comprise a peptide having an amino acid sequence with at least 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, and a peptide selected from the group of SEQ ID NO: 1 through SEQ ID NO: 34. No other limitations are present in the claims. The preamble is not given any patentable weight as it recites a desired outcome and does impose any specific limitations on the claims *per se*, as in a select patient population or specific therapy.

59. Janusz *et al.* teaches the administration nonapeptide (*Val-Glu-Ser-Tyr-Val-Pro-Leu-Phe-Pro*; identical to SEQ ID NO: 31 of the instant application) to mice (pp. 1030; Figures 1 &2).

Thus Janusz *et al.* teaches the administration to mice it meets the limitations of claims 1-3, 9, 14, 15, 16, and 17. Janusz *et al.* also meets the limitations of "a constituent peptide of colostrinin", "an active analog thereof", and SEQ ID NO: 31 thus meeting the limitations of claims 1, 6, 7, 9, 11, 12 (pp. 1029).

60. In regards to the asserted properties of colostrinin and its peptides, it has been established that a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore if colostrinin and constituent peptides such as nonapeptide indeed have the properties as asserted by the Applicant then these limitations are met and anticipated by Janusz *et al.*

61. In view of the desired outcome of the preamble, regardless of the desired or predicted out come, a reference which teaches the method steps anticipates the method [see *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.)]

62. Applicant may overcome this rejection by amending claims to remove the limitations which are taught by the reference.

63. Claims **1-4, 6, 9, 10, 11, 12, 14, 15, 16,** and **17** are rejected under 35 U.S.C. 102(b) as being anticipated by Inglot *et al.* (1996) "Colostrinine: a Proline-Rich Polypeptide from Ovine Colostrum Is A Modest Cytokine Inducer in Human Leukocytes." Archivum Immunologiae et Therapiae Experimentalis **44**(4): 215-224.

64. The claims are drawn to a method which comprises the step of contacting cells with a "neural cell regulator" therein defined as colostrinin, a constituent peptide thereof, an active analog thereof wherein said analog is required to comprise a peptide having an amino acid sequence with at least 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, and a peptide selected from the group of SEQ ID NO: 1 through SEQ ID NO: 34. No other limitations are present in the claims. The preamble is not given any patentable weight as it recites a desired outcome and does impose any specific limitations on the claims *per se*, as in a select patient population or specific therapy.

65. Inglot *et al.* teaches the oral administration proline-rich polypeptide (PRP) also known as colostrinine or colostrinin to humans (Abstract; pp. 219; Figures 1 & 2). Thus Janusz *et al.* teaches the administration of said peptides to humans it meets the limitations of claims 1-4, 9-11, 14, 15, 16, and 17. Inglot *et al.* meets the limitations of "colostrinin", "a constituent peptide of colostrinin", and "an active analog thereof" thus meeting the limitations of claims 1, 6, 9, 11 (pp. 1029).

66. In regards to the asserted properties of colostrinin and its peptides, it has been established that a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore if colostrinin indeed has the properties as asserted by the Applicant then these limitations are met and anticipated by Inglot *et al.*

67. In view of the desired outcome of the preamble, regardless of the desired or predicted out come, a reference which teaches the method steps anticipates the method [see *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.)]

68. Applicant may overcome this rejection by amending claims to remove the limitations which are taught by the reference.

Summary

69. Claims **1-17** are hereby rejected.

70. The Examiner respectfully notes that Applicant may submit a Notice of Appeal and an Appeal Brief in full response to this Office Action (MPEP §1205).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
May 5, 2004

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600